

REMARKS**1. REVIEW OF INTERVIEW AND RESPONSE TO IT BY APPLICANTS**

Applicant would like to thank Examiner Fubara for the courtesy of the in-person interview conducted on June 12, 2007. As reflected in the interview summary record, during the interview Applicant pointed out that Applicant's claimed composition is structurally different from that of the Muller reference (U.S. patent 5,624,972), and that these differences are directly related to the very different properties that each of Applicant and Muller seek to obtain. As Dr. Milbocker described at the interview, Muller is describing a foam mattress composition which requires a high quantity of free isocyanate to foam rapidly into a composition suitable for a mattress or other pad. In addition, Dr. Milbocker explained that, given the proposed use of Muller's composition, one skilled in the art would understand that Muller's use of a high percentage of hydrophilic propylene oxide (PO) is necessary and desirable to obtain a mattress that will not retain water.

As summarized in the interview summary record, Applicant's claimed composition distinguishes over Muller in that Applicant's composition:

- is a block copolymer polyol containing 10-30% PO
- contains at least 1% but no more than 5% free isocyanate.

These differences are structural distinctions in composition which define why Applicant's composition is a hydrogel forming adhesive which is compatible with tissue, and Muller's composition is not.

In rejecting the claims over Muller, the Examiner points in particular to Muller column 4, line 63 through column 5, line 5, which states:

Further particularly useful polyether polyols include polyoxypropylene diols and triols obtained by the simultaneous or sequential addition of ethylene and propylene oxides to di- or trifunctional initiators as fully described in the prior art. Random copolymers having oxyethylene contents of 10-80%, block copolymers having oxyethylene contents of from 2 to 30%, preferably from 5 to 25% and random/block copolymers having oxyethylene contents of up to 50%, based on the total weight of oxalkylene units may be mentioned.

The Examiner also points to Muller column 9, line 60 through column 10, line 3, which is Muller's description of a prepolymer Muller labels "MDI Polyisocyanate E". The cited description of Muller's MDI Polyisocyanate E is set forth below:

MDI Polyisocyanate E is a prepolymer (NCO=6.5%), prepared by reacting at 80 deg C. 25.7 pbw methylene diphenyldiisocyanate containing 10% of 2,4' isomer with 55.9 pbw of a propylene oxide/ethylene oxide (weight ratio 87/13) polyether triol of OH-value 36, and with 18.4 pbw of a propylene oxide/ethylene oxide polyether triol of OH-value 42, having a random PO/EO distribution in a weight ratio of about 25/75.

The product has a viscosity of 7500 cPs at 25 deg C. *The overall ethylene oxide content was about 28% on the basis of the total oxyalkylene residues.*

[emphasis added; see Muller U.S. patent 5,624,972 at column 9 line 60 through column 10, line 3.; "pbw" is "part(s) by weight"]

Significantly, in describing MDI Polyisocyanate E, Muller uses as one ingredient a polyol having a **random** PO/EO distribution of about 25/75, but *the overall content of EO in the MDI Polyisocyanate E was about 28%, i.e., the PO content was about 72% on the basis of the total oxyalkylene residues.*

As discussed at the interview and seen from the quoted portions of Muller from column 4-5, Muller proposes:

- (i) random copolymers having oxyethylene (EO) contents of 10-80% (Muller column 4, line 67 to column 5, line 1);
- (ii) block copolymers having oxyethylene (EO) contents from 2% to 30%, preferably from 5 to 25% (Muller col. 5, lines 1-2); and
- (iii) random/block copolymers having oxyethylene (EO) contents of up to 50% based on the total weight of oxyalkylene units (Muller column 5, lines 2-4).

Thus, the only block copolymer described by Muller has a low content of oxyethylene (EO), and a corresponding high percent of propylene oxide (PO) (98% to 70%). As shown below, with particular reference to the declaration of Dr. Milbocker submitted herewith, such compositions are not suitable for forming hydrogels. With respect to the portion of Muller cited at column 9-10, it is important to note that the prepolymer described at the bottom of column 9 contains as one ingredient or component "a propylene-oxide/ethylene oxide polyether triol...having a random PO/EO distribution in a weight ratio of about 25/75." Muller adds this component to other materials to make "MDI Polyisocyanate E." At column 10 lines 1-3, Muller tells us the overall ethylene oxide content of MDI Polyisocyanate E is 28%, i.e., the overall propylene oxide content is about 72%. Thus, the prepolymer, like Muller's other block prepolymers, contains over 70% PO.

In contrast, Applicant's claims, as amended, all define block polymer polyol compositions having a much lower propylene oxide (PO) content of 10% to 30% and at least 1% but less than 5% free isocyanate.

Independent claim 1, as amended, recites in pertinent part:

... wherein at least 1%-of said composition by weight, but not more than 5% of said composition by weight, comprises a low molecular weight free polyisocyanate, ...

... wherein on average in the composition 10% to 30% of the monomers of said block copolymer polyol are derived from propylene oxide monomers, and the rest of the monomers consist essentially of ethylene oxide derived monomers

Independent claim 17, as amended, recites in pertinent part:

...wherein at least one of said branched polyols consists of a copolymer of less than 10% polypropylene oxide and at least one of said branched polyols comprises a copolymer consisting of between about 10 and 30% polypropylene oxide monomers, the remainder of each of said branched polyols consisting essentially of ethylene oxide monomers,

... and wherein at least 1% of said solution but less than than 5% of said solution comprises free polyisocyanate

By specifying that one of the polyols has less than 10% PO and the other has 10% to 30% PO, the final composition is assured to have less than 30% PO as a fraction of the total alkylene content.

Independent claim 40, as amended, recites in pertinent part:

at least one block ethylene oxide-propylene oxide copolymer polyol, said composition comprising 10% to 30% propylene oxide monomers on average,

...

1% and less than 5% of said composition comprising free polyisocyanate

Independent claim 51, as amended, recites in pertinent part:

each said reacted polymer being a solvent for at least 1% but less than 5% by weight of a free low molecular weight organic polyisocyanate

...

wherein said liquid reactive component consists essentially of ethylene oxide and propylene oxide subunits and contains on average 10% to 30% propylene oxide

Independent claim 52, as amended, recites in pertinent part:

a block polyol having a tri-functional structure containing ethylene oxide and 10% to 30% propylene oxide

...

wherein the prepolymer composition contains at least 1% and less than 5% free polyisocyanate

Further clarifying amendments have been made to remove the N and (N-1) recitations, which appear to have caused some confusion. The claims have been amended to directly recite at least 1% and less than 5% free isocyanate. This range conforms to the specification (see, for example, paragraph [0052] of applicant's published application), was within the scope of the prior claim language, and is more limiting than the prior claim language. The amendment to recite "less than 5%" is to conform to the supporting disclosure, and is made for purposes of clarity, rather than for reduction of scope to avoid prior art. For clarity, the claims have also been amended to recite that the alkylene oxide monomers that are not propylene oxide are ethylene oxide monomers.

Submitted herewith is a second declaration of Dr. Milbocker, the Inventor. In his declaration, Dr. Milbocker explains the experimental basis for his conclusion, set forth at paragraphs [0045]-[0047] of the present application, that the amount of PO in the block copolymer polyol is important to making a hydrogel forming adhesive, and that the desired range of PO is 10% to 30%. Paragraphs [0045] – [0047] provide a concise summary of the important features recited in the amended claims.

[0045] The present invention relates to a 1-part surgical adhesive wherein covalent bonds are formed with body tissue and a hydrogel is formed of body fluids. However, the vast majority of NCO-terminated hydrophilic urethane prepolymers do not form such hydrogels. Urethane prepolymers are deemed hydrophilic if they incorporate in the urethane structure between 2 and 10% water. Such prepolymers are not effective as surgical adhesives since they are not hydrophilic enough and do not form hydrogels. Such prepolymers, when placed in an environment where the water exceeds 10% of the prepolymer volume polymerize internally without linking to tissue or fail to form a solid.

[0046] Consequently, the majority of hydrophilic polyether polyols can be excluded for use in the present invention. In particular, the polyol of

choice is a tri-functional form of PE/PO block polymer. The ratio of PE to PO is critical to the formation of the hydrogel. The PE provides the necessary hydrophilic nature, and the PO provides hydrogel strength. For example, adhesives formed from pure PE tend to breakdown in the body and swell to 2 to 10 times their original volume within several hours.

[0047] Adhesives of highest reliability will be non-absorbable and contain 10 to 30% PO. Adhesives with greater than 30% PO will not form hydrogels comprising greater than 50% water by volume.

The experiments described by Dr. Milbocker in his declaration show that a composition made in accordance with the claims, as amended (i.e., Milbocker Declaration paragraph 4, having 25% PO), makes a suitable hydrogel forming adhesive, and that a PO content of 50% (well above Applicant's upper limit of 30%) does not form a hydrogel and is not suitable as a tissue adhesive. Dr. Milbocker concluded that block copolymer polyols with a PO content above about 30% would not obtain suitable hydrogel forming adhesives, and that Muller's block copolymers with 70% or more PO would not form suitable hydrogel forming adhesives.

2. DETAILED RESPONSE TO PENDING REJECTIONS OF CLAIMS

With the above remarks in mind, Applicant responds to the outstanding rejections as follows.

Claims 1 – 3 and 8 stand rejected under 35 USC 102(b) over Muller et al, US 5,624,972, on the grounds that the compositions of Muller "meet" (describe the same composition as) Applicant's claims.

This rejection is respectfully traversed. After the amendments, each independent claim, and in case of ambiguity some of the dependent claims, refers to a block

copolymer, which never comprises more than 30% PO monomers, and has less than 5% free isocyanate.

Hence, for example, Applicant's polymers are block copolymers containing 10-30% PO (propylene oxide), and the rest (90% to 70%) EO (ethylene oxide), as recited in claims 1, 40, 51 and 52; or can be a mixture of block copolymers, one containing less than 10% PO and another containing 10-30% PO (claim 17), for example 5% and 25% PO (claim 18); or a 25%:75% PO:EO (claim 30). Their block nature is recited as an explicit limitation in each of these independent claims.

When Muller uses block copolymers they are rich in PO (propylene oxide), having an EO (ethylene oxide) content of 2 – 30% (i.e., PO content of 98% - 70%), as described by Examiner. **The Muller PO range of 98% - 70% in block copolymers is distinct from the Applicant's PO range of 10-30%.** It is believed, based on discussion at the Interview of June 12, that Examiner and applicant are in agreement that these ranges are sufficiently distinct, and have sufficient and discernable differences in properties to describe materials that are distinct both in composition and in behavior.

Muller also sometimes uses a small proportion of random copolymers of EO and PO with a very wide range of monomer ratios, having "oxyethylene contents ranging from 10% to 80%" (Muller et al col 4 line 67 – col. 5 line 1). Muller mixes in such random polymers with high-PO content block copolymers, but only in proportions so that the overall PO content remains above 70% by weight.

For example, in the preparation of Muller's MDI polyisocyanate E, col 9 line 60 – col 10 line 3, 18.4% by weight of a random high-EO polymer (25:75 PO/EO) is added to 55.9% of a copolymer with an PO:EO weight ratio of 87/13, very high in PO. The final mixture, after isocyanate capping, had an EO percentage of 28% on a basis of number of residues, and hence had 72% PO by number (and more by weight). This product of Muller is far outside of applicant's range of mixtures ready for polymerization as tissue

adhesives. Moreover, applicant uses block copolymers, not random copolymers, even when mixing copolymers to obtain desired effects, as in claim 17.

At col. 9 lines 45 – 49, Muller lists polyisocyanate A, which is a reaction product of 250 parts isocyanate with 750 parts of an “ethylene oxide tipped polyoxypropylene triol”. This chemical description is indicative of a block copolymer – a central PO core with EO blocks on the end – and as a block polymer, the material will have a PO content of 70 – 98% by weight. In fact, the final PO percentage in the composition is still over 70% PO even after dilution of the high PO block copolymer with high-EO random polymer, according to Muller.

Polyisocyanate D is the same material with some isophorone diamine added.

Polyisocyanate F has a polymeric component having 10.9% of EO (89.1% PO) “by tipping” – i.e., block (PO center and EO ends).

Polyisocyanates B, C, and G are mixtures of low MW isocyanates – e.g. MDI – with higher isocyanate oligomers; they do not contain polyols.

Hence, Muller does not describe any block polyol preparation ready for polymerization where the polymer is comprised of less than 70% PO groups. In some instances Muller uses ingredients in a preparation ready for polymerization with high proportion of EO. However, in these preparations Muller uses only random copolymers containing high proportions of EO as ingredients, which are distinct from Applicant’s block copolymers. Even in mixtures of random copolymers containing high proportions of EO, the overall PO content of these mixtures was more than 70% PO.

In examples 1 – 7, Muller uses the above components to make conventional dry polyurethane foams. He mixes from about 1 up to 4.8 pbw (parts by weight) water, containing less than 1 pbw (relative to the final composition) catalyst, with 100 parts by weight of combined isocyanates (part polymeric, part low molecular weight). The procedure is described in general at the top of col. 9, and in detail in Example 7. The blended isocyanate mix is forcibly blended at high shear with the water and catalysts, and immediately placed, as a “creaming” mixture, onto a slab. Muller does not bother to

explain, since it is well known, that the creaming mixture looks "creamy" because of bubbles of CO₂ (carbon dioxide) formed when the isocyanate – especially the excess of low molecular weight isocyanate - and water mix. As the foam expands, the polymers are crosslinked, and when the bubbles break, the crosslinked polymeric isocyanates form the strands of a conventional flexible polyurethane foam.

This is all that is enabled in Muller, and all that is described. Muller nowhere discloses the sort of high EO block copolymers that Applicant uses, and which are essential for forming hydrogels. In the second Declaration of the Applicant, examples of ready for polymerization compositions containing 50:50 EO/PO (i.e., 50% of the alkylene oxide monomers in the final composition being PO) in one example, and 75:25 EO/PO (i.e., 25% of the alkylene oxide monomers being PO) in another example, are compared with respect to their ability to form hydrogels when the ready for polymerization compositions are mixed 1:1 by volume with water, in order to polymerize them.

In the example containing 50:50 EO/PO the polymeric fraction separated from the water fraction, creating a dry foam with the water excluded. In the example containing 75:25 EO/PO the polymeric fraction did not separate from the water fraction, creating a wet hydrogel containing 50% water, with no free water in the final composition. Applicant concludes from this experiment that the hydrophobic nature of the propylene oxide (PO) fraction prevents the formation of a hydrogel by exclusion of water during the polymerization process when PO concentration is greater than 50%. Muller never makes a mixture that is under 70% PO, even when occasionally small proportions of higher EO-content random copolymers are used in the mixture.

In addition to the composition of the copolymers, Muller et al differs in the amount of "free" (low molecular weight) isocyanate in the preparation. Applicants are limited to about 5% or less in their claims and specification. Muller always uses a large excess of low MW isocyanate (at least 10% in the examples, and usually 25% or more) in the mixture, in order to provide a rapid creation of foam upon reaction with a relatively small amount of water. The large excess of low MW isocyanate in combination with water creates a blowing agent intended to substitute for halocarbon blowing agents.

In Muller's preferred reaction system, beginning at col 7 line 64, A is an isocyanate terminated prepolymer with an NCO content of 2 to 15% by weight; B is a diphenylmethane diisocyanate compound (low molecular weight or "free" isocyanate) having at least 20% NCO by weight; plus a component C containing water and (col 8 line 14-15) comprising 1 to 5% of the weight; wherein A + B together contain 20 to 40% polyphenylisocyanates or residues thereof, and 80 to 60% of residues of isocyanate-reactive species.

In other words, the composition originally contained 20% to 40% by weight of a low molecular weight isocyanate such as diphenylmethane diisocyanate.

In Muller Col 9 – 10, MDI-polyisocyanates A through G are defined. B, C and G are various low molecular weight isocyanate mixtures. A, D, E and F are isocyanate tipped polymeric polyols with leftover isocyanate. The starting ratio of polyol to isocyanate is 750:250 (A); 752:321 (D), 74.3:27.3 (E), and 73.2: 26.8 (F), which is each case is about 75% or less polyol and 25% or more isocyanate.

Every one of the polymer-containing preparations has a large excess of free isocyanate. In use, they are mixed with more low molecular weight isocyanate:

Example 1, 80 parts polymer/isocyanate mix (A), 10 parts each isocyanates B and C;

Example 2, 90 parts polymer/isocyanate mix A, 10 parts isocyanate B;

Example 3, 90 parts polymer/isocyanate mix D, 10 parts isocyanate C;

Example 4, 90 parts polymer/isocyanate mix E, 10 parts "Suprasec" (isocyanate C; col 9 line 54);

Example 5, 90 parts polymer/isocyanate mix F, 10 parts Suprasec/ isocyanate C;

Example 6, 90 parts polymer/isocyanate mix A, 10 parts isocyanate G.

Example 7 describes the process of conversion of the materials of example 1 into a foam. The isocyanates and polymers are blended 2.5 cm into a mixing head, then, at the 15cm level in the mixing head (col 12 line 37), the catalysts are added; then, at the 17 cm level, water is added (line 42), and at the 50 cm level (line 32), the creaming mixture

is ejected (line 49 – 52). Thus, in Muller the mixture before adding water clearly has a concentration of isocyanates not bonded to polyols of greater than 10%, and probably even greater, since the ratio of isocyanate to polyol, in the polymer mixtures A, D, E, and F, before adding isocyanates B, C, G, is 25%:75% - 25 g. isocyanate to 75 g. polyol, or 25% of the solution being free isocyanate (or low polymers of the isocyanate with itself).

Thus, in every example of Muller, the percentage of free isocyanate is over 10%, and probably considerably higher. This is much higher than Applicant's claimed compositions, which all require between 1% and 5% free isocyanate.

In contrast, Applicants claim:

1. (currently amended) A biocompatible hydrogel-forming tissue-bonding adhesive composition, the composition comprising:

one or more block copolymer polyols, wherein each hydroxyl of said block copolymer polyols is terminated with a low molecular weight polyisocyanate, said terminated block copolymer polyols being liquid and water-soluble;

and wherein said block copolymer polyols have a functionality averaging N at least 1.5, and at least 1% ~~-(N-1)%~~ of said composition by weight, but not more than 5% of said composition by weight comprises a low molecular weight free polyisocyanate, which may be the same as the polyisocyanate terminating the block copolymer polyols;

and wherein on average in the solution 10% to 30% of the monomers of said block copolymer polyols are derived from propylene oxide monomers;

characterized in that after polymerization, upon exposure to tissue or water, the adhesive forms a hydrogel comprising, after equilibration with water or aqueous fluids, greater than 50% water by volume; and

wherein the composition polymerizes in situ upon exposure to water and application to tissue, without requiring the addition of a catalyst.

This composition is distinctly different from Muller in several aspects:

1. the overall percentage of PO:

30% or less for Applicant,

70% or more for Muller;

2. the structure of the high EO polymers:

Block high % EO for Applicant

Random high % EO for Muller, in limited quantity

3 . the percent "free" low molecular weight isocyanate in the preparation, at the time of polymerization to form the product, is:

less than 5% for Applicant;

at least about 10% for Muller, and perhaps as high as 35%.

(This is clear once one notes that the polymer preparations A, D, E and F each contain 25% or more by weight of low molecular weight isocyanate.)

4. the use of catalysts:

Applicant does not use catalyst,

Muller always uses catalysts.

5. the polymerization products are different:

Applicant's compositions take up at least 50% by volume water to form a hydrogel;

Muller's compositions form dry foams, wherein a little water is used in combination with large amounts of free low molecular weight isocyanate to form a blowing agent for foam creation.

In summary, there are clear distinctions between the compositions of Applicant and Muller, which are found in applicant's specification and claims; and, the differences are functional, so that the materials have significantly different properties.

OTHER ISSUES

Examiner on p. 3 line 5 cites "80:20 EO:PO" at Muller col. 9 lines 46-47. The reference at this location actually describes "an 80:20 mixture of 4,4' – and 2,4'-MDI", i.e., the ratio of isomers of the low MW isocyanate. The reference does not support a block EO:PO copolymer falling within applicant's claimed range. The same difficulty is found on p. 3 lines 9, 10 of the action, just before the conclusion that "Muller meets the limitations of Claims 1-3 and 8."

In light of all of the above, the rejection of claims 1-3 and 8 as anticipated by Muller is respectfully traversed. The passage of these claims to issue is respectfully requested.

REJECTIONS UNDER 103

Rejection of claims 5-7, 9-14, 17-30, 40-42, and 44-48 under section 103 as obvious over Muller et al. None of these claims stand rejected under section 102.

The rejection under sect. 103 is because the random copolymer used in some examples of Muller is comprised of a composition that has PO in the range of 25%, as described in Muller at col. 9 line 67, and therefore falls within the numerical limits of applicant's claims. (This appears to be the same issue that has been discussed above in the 102 rejection.)

This rejection is traversed on two grounds. First, the Muller polymer in question is random, not block; all of applicant's claims contain, or depend on claims containing, a restriction to block copolymers. Selection criteria for PO:EO alkylene oxides are found in various places in applicant's specification, for example at least in para. 0034, 0045 – 47. Polymers with PO contents over 30% are explicitly rejected at para. 0047.

Secondly, the mixture that is polymerized in Muller is always above about 70% in PO monomers. Small additions of high EO polymers do not reduce the high PO content or change the dominantly hydrophobic nature of Muller's preparations, and none of Muller's preparations ready for polymerization are suitable for applicant's uses. Muller does not polymerize (mix with water) any mixture of polymers containing less than 70% PO, and the inclusion of a small amount of random EO:PO copolymer outside that range does not motivate one to try an overall 75% EO polymer to make foam. (And if tried, it would not form a suitable dry foam – instead, it would absorb water from the atmosphere and eventually become a wet gel.) Applicant's materials are not suggested in Muller itself, and Muller teaches away from applicant's preparation by always polymerizing compositions having about 70% or more of PO, even if some component species in the mixture have less.

There are other differences, as noted under the 102 rejection, which separately support the distinctness of applicant's composition over that of Muller, and thus support the patentability of applicant's composition. These differences are, in addition to the percent of PO in the mixture, the block polymer nature of applicant's high EO polymers, vs. Muller's random structure; the overall level of free isocyanate, about 2X to 5X higher than applicants; the use of catalyst by Muller but not applicants; and most importantly, the formation of hydrogels by Applicant's formulation, vs. the formation of dry foam by Muller's formulation.

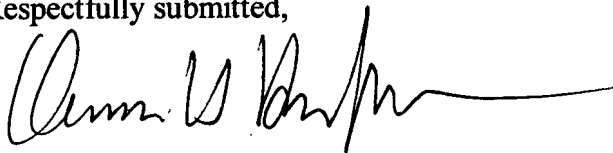
It is not obvious to try something that one *knows* would be useless for the intended purpose, and Muller's compositions are useless for applicant's purposes, and conversely applicant's compositions are useless for Muller's purposes. Moreover, as recited in the second Declaration, Applicant was aware of this distinction (that high PO content was unsuitable for Applicant's hydrogel-forming adhesives) at the time of the original filing of the present application.

Accordingly, the rejection of claims 5-7, 9-14, 17-30, 40-42, and 44-48 under 103 as obvious over Muller et al. is respectfully traversed, and the passage of these claims to issue is requested.

Claims 49 – 52, including independent claims 51 and 52, do not stand rejected. Even if they had been rejected, the same reasoning as above would make these claims novel and non-obvious over Muller. Passage of these claims to issue is respectfully requested.

Examiner is urged to contact applicants by telephone to resolve any formal or other issues that might stand in the way of allowance of claims in this application.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Francis H Kirkpatrick', with a long horizontal flourish extending to the right.

Francis H Kirkpatrick (35,219) 978-790-7186